

C. Remarks

The claims are 1-15, with claims 1, 8 and 11 being independent. The independent claims have been amended to better define the present invention. Support for this amendment may be found, *inter alia*, in the originally filed specification at page 7, lines 13-15. Claims 2, 6, 7, 9, 10, 14 and 15 have been amended solely as to form. A second substitute specification is submitted herewith to make additional formal changes in the text of which errors Applicants have now become aware. A marked-up copy of the original specification showing the changes made thereto in both substitute specifications is attached. No new matter has been added. Reconsideration of the claims is expressly requested.

Claims 1-5 stand rejected under 35 U.S.C. § 102(e) as being allegedly anticipated by U.S. Patent Application No. 2005/0272169 A1 (Griffin). Claims 4, 5 and 8 stand rejected under 35 U.S.C. § 103(a) as being allegedly obvious from Griffin. Claims 6, 7, 9, 10, 14 and 15 stand rejected under 35 U.S.C. § 103(a) as being allegedly obvious from Griffin in view of U.S. Patent No. 6,432,719 B2 (Vann). The grounds of rejection are respectfully traversed.

Prior to addressing the merits of rejection, Applicants would like to briefly discuss some of the features and advantages of the presently claimed invention. That invention is related, in pertinent part, to a biochemical reaction cartridge and to a method and system utilizing this cartridge. The biochemical cartridge in accordance with the claimed invention includes a reaction portion and a solution storage portion, which is separated from the reaction portion.

Importantly, the solution storage portion is superposed on the reaction portion at the time of use, so that the solution is moved from the solution storage portion to the reaction portion through a penetrable partition member. Due to this arrangement, it is possible to achieve superior results, such that only the solution storage portion can be stored in a cold place and that different solution storage portions can be independently used in combination with a common reaction portion depending on the purpose of the analysis performed using the cartridge.

Griffin is directed to a biochemical analysis device. It discloses that an intermediate layer is provided between a solution storage chamber containing a solution and a reaction chamber, and the solution is moved from the solution storage chamber to the reaction chamber by breaking the intermediate layer by a pin, a projection, pressurization, or heating. However, Applicants respectfully submit that Griffin fails to disclose or suggest a cartridge in which, at the time of use, the solution storage chamber is superposed on the reaction chamber.

Vann cannot cure the deficiencies of Griffin. Specifically, like Griffin, Vann does not teach a cartridge in which, at the time of use, the solution storage chamber is superposed on the reaction chamber.

Accordingly, whether considered separately or in combination, Griffin and Vann cannot affect the patentability of the presently claimed invention. Wherefore, withdrawal of the outstanding rejections and expedient passage of the application to issue are respectfully requested.

Applicants' undersigned attorney may be reached in our New York office by telephone at (212) 218-2100. All correspondence should continue to be directed to our address given below.

Respectfully submitted,

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BIOCHEMICAL REACTION CARTRIDGE

FIELD OF THE INVENTION AND RELATED ART

The present invention relates to a biochemical
5 reaction cartridge ~~used to~~ that can be incorporated in
an apparatus for analyzing a cell, a microorganism, a
chromosome, a nucleic acid, etc., in a specimen by
utilizing a biochemical reaction, such as
antigen-antibody reaction, or nucleic acid
10 hybridization.

Most ~~of~~ analyzers for analyzing specimens, such
as blood, uses an immunological procedure utilizing an
antigen-antibody reaction or a procedure utilizing
nucleic acid hybridization. For example, protein or
15 single-stranded nucleic acid, such as antibody or
antigen, which specifically ~~connects~~ hybridizes with a
material or substance to be detected, is used as a
probe and is fixed on a surface of a solid phase, such
as fine particles, beads or a glass plate, thus
20 effecting the antigen-antibody reaction or nucleic
acid hybridization. Then, for example, an
antigen-antibody compound or double-stranded nucleic
acid is detected by a labeled antigen or labeled
nucleic acid, which causes a specific interaction,
25 such that a labeled material having a high detection
sensitivity, such as an enzyme, a fluorescent material
or a luminescent material, is supported, thus

effecting detection of presence or absence of the material to be detected or a quantitative determination regarding the detected material.

As an extension of these technologies, e.g., U.S. Patent No. 5,445,934 ~~has disclosed~~ discloses a so-called DNA (deoxyribonucleic acid) array, wherein a large number of DNA probes having mutually different base sequences are arranged on a substrate in an array form.

Further, Anal. Biochem., 270(1), pp. 103 - 111 (1999) ~~has disclosed~~ discloses a process for preparing a protein array, like the DNA array, such that various species of proteins are arranged on a membrane filter. By using these DNA and protein arrays and the like, it has become possible to ~~effect a test on a~~ large number of items at the same time.

Further, in various methods of the specimen analysis, in order to ~~realize alleviation~~ alleviate of the contamination by the specimen, ~~promotion~~ promote of reaction efficiency, ~~reduction~~ reduce in the size of the apparatus-size, and ~~facilitation~~ facilitate of the operation, there have been also proposed disposable biochemical reaction cartridges in which a necessary reaction is performed ~~in the cartridge~~. For example, Japanese Laid-Open Patent Application (JP-A) (Tokuhyo) Hei 11-509094 ~~has disclosed~~ discloses a biochemical reaction cartridge, including DNA array,

in which a plurality of chambers are disposed and a solution is moved by a differential pressure, so as to permit a reaction, such as extraction, amplification or hybridization of DNA in a specimen, within the
5 cartridge.

As a method of supplying a reagent with respect to the biochemical reaction cartridge, JP-A 2000-266759 ~~has disclosed~~ discloses that a reagent is supplied from an external reagent bottle to a
10 disposable analysis cassette. Further, JP-A (Tokuhyo) Hei 11-5059094 ~~has disclosed~~ discloses that a reagent is incorporated in a chamber in advance.

However, in the case of externally supplying the reagent, a plurality of reagents must be prepared
15 separately from the biochemical reaction cartridge, and if the number of test items is large, the number of necessary reagents is also increased. As a result, replenishment of the reagents becomes complicated and there is a possibility of erroneously selecting the
20 species of the reagents. Further, when ~~in the case of incorporating the reagent is incorporated into the~~ chamber of the biochemical reaction cartridge, ~~there it is a possibility possible such~~ that a reaction different from ~~an~~ that intended ~~reaction is caused~~
25 ~~to~~ can occur ~~by flowing of if~~ the reagent flows ~~in the chamber~~ into a passage or another chamber due to an environmental change at the time of storage or

conveyance ~~or vibration~~ during conveyance.

SUMMARY OF THE INVENTION

An object of the present invention is to provide
5 a biochemical reaction cartridge, having solved the
~~above~~ above-described problems, which eliminates the
inconvenience of replenishment of a reagent and
erroneous selection of the species of reagent and
~~causes no flowing of~~ does not cause the reagent in a
10 chamber to flow into a passage or vibration at the
time of storage or conveyance.

Another object of the present invention is to
provide a biochemical reaction apparatus for effecting
a biochemical reaction by using the biochemical
15 reaction cartridge.

According to the present invention, there is
provided a biochemical reaction cartridge, comprising:

a reaction portion, comprising a chamber and a
passage, for effecting a biochemical reaction, and
20 a solution storage portion, which is isolated or
separated from the reaction portion, for storing a
solution ~~in~~ at a position corresponding to the
chamber,

wherein the cartridge is provided with a
25 penetrable partition member disposed between the
solution storage portion and the reaction portion so
as to move the solution from the solution storage

portion to the chamber of the reaction portion.

These and other objects, features and advantages
of the present invention will become more apparent
upon a consideration of the following description of
5 the preferred embodiments of the present invention
taken in conjunction with the accompanying drawings.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a perspective view of an embodiment
10 of the biochemical reaction cartridge according to the
present invention.

Figure 2 is a plan view of a solution storage
portion.

Figure 3 is a partial sectional view of the
15 biochemical reaction cartridge at the time of storage.

Figure 4 is a partial sectional view of the
biochemical reaction cartridge in such a state that a
valve stem (rod) is pressed by first-stage pushing.

Figure 5 is a partial sectional view of the
20 biochemical reaction cartridge in such a state that a
valve stem is pressed by second-state pushing.

Figure 6 is a plan view of a reaction portion.

Figure 7 is a block diagram of a treatment
apparatus for controlling the movement of a solution
25 and various reactions within the biochemical reaction
cartridge.

Figures 8A and 8B ~~is~~ show a flow chart of a first

treatment procedure.

~~Figure~~ Figure 9 is a longitudinal sectional view of a part of the chambers shown in Figure 6.

Figure 10 is a longitudinal sectional view of
5 another part of the chambers shown in Figure 6.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

~~Hereinbelow~~ Below, the present invention ~~will be~~ is
described more specifically with reference to the
10 drawings.

Figure 1 is a perspective view of a biochemical reaction cartridge in this embodiment. Referring to Figure 1, the cartridge has a two-layer structure including a reaction portion 1, where a reaction is
15 effected, and a solution storage portion 2 disposed thereon for storing solutions, such as a reagent and a cleaning agent.

A body of each of the reaction portion 1 and the solution storage portion 2 comprises a synthetic
20 resin, such as polymethyl methacrylate (PMMA), acrylonitrile-butadiene-styrene (ABS) copolymer, polystyrene, polycarbonate, polyester or polyvinyl chloride. In the case where an optical measurement is required, the material for the body of the reaction
25 portion 1 is required to be a transparent or semitransparent plastic.

At an upper portion of the reaction portion 1, a

specimen port 3 for injecting a specimen, such as blood, by a syringe (injector) is disposed and sealed up with a rubber cap. On both side surfaces of the reaction portion 1, there is a plurality of nozzle
5 ports 4, into which nozzles are injected to apply or reduce pressure in order to move a solution in the reaction portion 1. A rubber cap is fixed on each of the nozzle ports 4. The other side surface of the reaction portion 1 has a similar structure.

10 Further, to an upper portion of the solution storage portion 2, 3 aluminum foil sheets are applied for blocking an upper portion of a solution storage chamber described later. The reaction portion 1 and the solution storage portion 2 are bonded to each
15 other through ultrasonic fusion. Incidentally, the reaction portion 1 and the solution storage portion 2 are separately prepared, and the solution storage portion 2 may be superimposed on the reaction portion 1 at the time of use.

20 ~~To the side surface of the biochemical reaction cartridge,~~ a A bar code label 40 for identifying the type of cartridge is adhered to the side surface of the biochemical reaction cartridge. When the biochemical reaction cartridge is set to a treatment
25 apparatus described later, the bar code is read and the type of the cartridge is identified from the result. Setting of the treatment apparatus is

automatically performed, so as to effect an appropriate treatment procedure.

Figure 2 is a plan view of the solution storage portion 2 of Figure 1. Referring to Figure 2, the solution storage portion 2 is provided with independent chambers 6a to 6m, each containing a solution. In the chambers 6 and 6b, a first hemolytic agent containing EDTA (ethylenediaminetetraacetic acid) for destructing cell ~~wall~~-membrane and a second hemolytic agent containing a ~~protein~~-protein-modifying agent, such as a surfactant, are stored, respectively.

In the chamber 6c, particles of magnetic material coated with silica, by which DNA is adsorbed, are stored in the chamber 6g. In the chambers 6l and 6m, a first extraction cleaning liquid and a second extraction cleaning liquid, which are used for purifying DNA at the time of extraction of DNA, are stored, respectively.

An eluent, comprising a buffer of low concentration salt, for eluting DNA from the magnetic particles, is stored in the chamber 6d, ~~a.~~ A mixture liquid for PCR (~~polymerase~~-polymerase chain reaction) comprising a primer, polymerase, a dNTP (deoxyribonucleotide triphosphate), a buffer, Cy-3dUTP containing a fluorescent agent, etc., is stored in the chamber 6g. In the chambers 6h and 6j, a cleaning agent containing a surfactant for cleaning a

fluorescence-labeled specimen DNA, which is not
subjected to hybridization, and a fluorescence label
are stored. In the chamber 6i, alcohol for drying the
inside of a chamber including a DNA microarray, which
5 is described laterbelow, is stored. The respective
chambers 6a to 6m are provided with a sharp-pointed
valve stems (rods) 7a to 7m, respectively, described
laterbelow, for penetrating the sheets.

Figure 3 is a sectional view showing a storage
10 state in the biochemical reaction cartridge.
Referring to Figure 3, the valve stem 7 provided with
a cut 8 is injected into the chamber 6, ~~containing a~~
~~solution,~~ of the solution storage portion 2, which
contains a solution, ~~the valve stem 7 provided with a~~
15 ~~cut 8 is injected and~~ is supported by two o-rings.
The bottom of the solution chamber 6 is blocked by an
aluminum foil sheet 10. A sealing member 12 is
disposed between the chamber 6 and the chamber 11 of
the reaction portion 1, so as to make it impossible
20 for air to enter and exit. Changes in volume of the
solution and air and in pressure due to the
environment can be ~~adsorbed~~ accommodated by the
deformation of the aluminum foil sheet 10, so that the
solution in the chamber 6 cannot unexpectedly enter
25 the reaction portion 1.

Figure 4 illustrates ~~such a state that~~ in which,
after a tester injects a liquid specimen, such as

blood, from the specimen port 3 and sets the biochemical reaction cartridge to a treatment apparatus described ~~later~~below, a robot arm (not shown) presses the valve stem 7 by first-stage pushing
5 with a shorter pressing rod 13a of a rod needle 13 to ~~stare~~tear the aluminum foil sheet, thus starting the movement of the solution from the chamber 6 to the chamber 11. In this state, the two O-rings ~~8-9~~are located in the cut 8 of the valve stem 7, so that the
10 chamber 6 communicates with outside air. Accordingly, the solution can be moved smoothly.

As described above, the biochemical reaction cartridge has the penetrable aluminum sheet 10 as a partition member, so that only by ~~the~~-pressing the
15 pressing rod 13a of the tool needle 13 toward the reaction portion 1, it is possible to readily cause the solution to flow from the chamber 6 into the chamber 11 without ~~causing contact of the tool needle~~
13 coming into contact with the solution.
20 Incidentally, in this embodiment, immediately under the position of the chamber of the solution storage portion 2, a corresponding chamber of the reaction portion 1 is located, but there is no harm in shifting the corresponding chamber from the position
25 immediately under the chamber of the solution storage portion 2 if, e.g., a passage is provided therebetween.

In this embodiment, the chamber of the reaction portion 1 and the chamber of the solution storage portion 2 are in a one-to-one relationship, but a plurality of solution storage chambers may be provided per one chamber for the reaction portion 1. Further, in this embodiment, the solution is moved from the solution storage chamber to a blank chamber of the reaction portion 1, but it may be moved from the solution storage chamber to a chamber of the reaction portion 1 already containing a specimen or a solution during treatment. Further, in this embodiment, the aluminum foil sheet 10 is used as the partition member, but the partition member per se may be a non-penetrable member if it is provided with an ordinary valve, and the valve is placed in a penetrable state, i.e., an open state so as to permit the flowing of the solution into the chamber of the reaction portion 1.

Next, the tester ~~once~~ extracts the tool needle 13 from the treatment apparatus once by using the robot arm and turns the tool needle 13 upside down, followed by further pressing the valve stem 7 by second-stage pushing with a longer pressing rod 13b, as shown in Figure 5. As a result, air is sealed up by the upper O-ring 9 ~~to permit movement of the solution in the reaction portion 9~~ to permit the movement of the solution in the reaction portion 1, as described

~~later~~below. The tester performs this step with respect to all the chambers 6a to 6m. As described above, the solution can be caused to flow into the chamber by the first-stage pushing, and the chamber
5 can be sealed up by the second-stage pushing, so that it is possible to effect the ~~flowing~~ of the solution into the chamber 11 and ~~sealing off~~ the chamber 11 ~~at the same time~~ only by simple pushing operations. Further, the above-described tool needle may be
10 provided in the biochemical reaction cartridge.

Figure 6 is a plan view of the reaction portion 1. Referring to Figure 6, ~~on one side surface of the reaction portion 1~~, 10 nozzle ports 4a to 4j are provided on one side surface of the reaction portion
15 ~~and also o.~~ On the other side surface thereof, 10 nozzle ports 4k to 4t are provided. The respective nozzle ports 4a to 4t communicate with chambers 11a to 11t, which are portions or sites for storing the solution or causing a reaction, through corresponding
20 air passages 14a to 14t for air flow, respectively.

In this embodiment, however, the nozzle ports 4n, 4p, 4q and 4s are not used, ~~t.~~ These nozzle ports do not communicate with the chambers and are used as reserve ports. More specifically, in this embodiment,
25 the nozzle ports 4a to 4j communicate with the chambers 11a to 11j through the passages 14a to 14j, respectively. On the other side surface, the nozzle

ports 4k, 4l, 4m, 4o, 4r and 4t communicate with the chambers 11k, 11l, 11m, 11o, 11r and 11t through the passages 14k, 14l, 14m, 14o, 14r and 14t, respectively.

5 The specimen port 3 communicates with a chamber 16. The chambers 11a, 11b, 11c and 11k communicate with the chamber 16, the chambers 11g and 11o communicate with a chamber 17, and the chambers 11h, 11i, 11j, 11r and 11t communicate with a chamber 18.
10 Further, the chamber 16 communicate with the chamber 17 via a passage 19, and the chamber 17 communicates with the chamber 18 via a passage 20. With the passage 19, the chambers 11d, 11e, 11f, 11l and 11m communicate via passages 15d, 15e, 15f, 15l and 15m,
15 respectively. At a bottom (undersurface) of the chamber 18, a square hole is provided. ~~To the square hole, a~~ A DNA microarray 21, on which several tens to several hundreds of thousand of different species of DNA probes are arranged ~~in~~ at high density on a
20 surface of a solid phase, such as a glass plate having a size of ca. one square centimeter, with the probe surfaces up, is attached to the square hole.

It is possible to test a large number of genes at the same time by ~~effecting a hybridization reaction~~ ing
25 with the specimen DNA ~~with the use of~~ using the microarray 21.

The DNA probes are regularly arranged in a

matrix form, and an address (position determined by
the row and column numbers ~~of row and the number of~~
~~column~~ on the matrix) of each of the DNA probes is
readily read as information. The genes to be tested
5 includes, e.g., genetic polymorphism of each
individual in addition to infections viruses, bacteria
and disease-associated genes.

In the chambers 11a and 11b of the reaction
portion 1, a first hemolytic agent and a second
10 hemolytic agent to be moved from the chambers 6a and
6b, and the solution storage portion 2 are stored,
respectively. In the chamber 11c, magnetic material
particles ~~of magnetic material~~ to be moved from the
chamber 6t are stored. In the chambers 11l and 11m, a
15 first extraction cleaning liquid and a second
extraction cleaning liquid to be moved from the
chambers 6l and 6m are stored, respectively. An
eluent flowing from the chamber 6d is stored in the
chamber 11d, a mixture liquid necessary for PCR
20 (~~polymerase~~ polymerase chain reaction) moved from the
chamber 6g is stored in the chamber 11g. In the
chambers 11h and 11j, cleaning agents to be moved from
the chambers 6h and 6j are stored, respectively. In
the chamber 11i, alcohol to be moved from the chamber
25 6i is stored.

The chamber 11e is a chamber in which ~~dust~~ debris,
other than DNA ~~of~~ from blood, accumulates, the chamber

11f is a chamber in which waste of the first and second extraction cleaning liquids in the chambers 11l and 11m accumulates, the chamber 11r is a chamber in which waste of the first and second cleaning agents
5 accumulates, and the chambers 11k, 11o and 11t are blank chambers provided for preventing the solution ~~to~~ from flowing into the nozzle ports.

Figure 7 is a schematic view of the treatment apparatus for controlling the movement of the solution
10 within the biochemical reaction cartridge and various reactions.

~~On a table 22, the~~ The biochemical reaction cartridge is mounted on a table 22. Further, ~~on the table 22,~~ an electromagnet 23 to be actuated at the
15 time of extracting DNA or the like from the specimen in the cartridge 1, a Peltier element 24 for effecting temperature control at the time of amplifying DNA from the specimen through a method such as PCR (polymerase chain reaction), and a Peltier element 25 for
20 effecting temperature control at the time of performing a hybridization between the amplified specimen DNA and the DNA probe on the DNA microarray within the cartridge 1 and at the time of cleaning or washing the specimen DNA, which is not hybridized, are
25 disposed on the table 22 and connected to a control unit 26 for controlling the entire treatment apparatus. Further, the robot arm (not shown) for

pushing down the valve stem by moving the tool needle
13 above a predetermined chamber on the cartridge, as
described above, and a bar code reader (not shown) for
reading the bar code label applied to the cartridge
5 are provided ~~to~~ in the treatment apparatus.

At both side surfaces of the table 22, an
electric (motor-driven) syringe pumps 27 and 28 and
pump blocks 31 and 32, each of which is a port for
discharging or sucking in air by these pumps 27 and 28
10 and is provided with 10 pump nozzles 29 or 30 on its
side surface, are disposed. Between the electric
syringe pumps 27 and 28 and the pump nozzles 29 and
30, a plurality of known electric switching (selector)
valves (not shown) are disposed and connected to the
15 control unit 26 together with the pumps 27 and 28.
The control unit 26 is connected to an input unit 33
to which inputting by a tester is performed. The
control unit 26 controls the pump nozzles 29 and 30,
so that each of the respective 10 pump nozzles is
20 selectively opened and closed with respect to the
electric syringe pumps 27 and 28, respectively.

When the solution is moved from the solution
storage portion 2 to the reaction portion 1 and a
treatment start signal is inputted, extraction and
25 amplification of DNA or the like are performed within
the reaction portion 1. Further, hybridization
between the amplified specimen DNA and DNA probes on

the DNA microarray disposed in the reaction portion 1 and cleaning of the fluorescence-labeled specimen DNA, which is not hybridized, and the fluorescence label are performed.

5 In this embodiment, when the tester injects blood as a specimen into the reaction portion through the rubber cap of the specimen port 3 by a syringe or an injector, the blood flows into the chamber 16. Thereafter, the tester places the biochemical reaction
10 cartridge on the table 22 and moves the pump blocks 31 and 32 in directions indicated ~~of~~ by the arrows ~~indicated~~ in Figure 7 with a mechanism (not shown) by operating ~~an unshown~~ a lever (not shown), whereby the pump nozzles 29 and 30 are injected into the
15 corresponding nozzle ports 4 of the reaction portion 1.

 As described with reference to Figure 6, the nozzle ports 4 are concentrated at two surfaces, i.e., both side surfaces, of the biochemical reaction
20 cartridge, so that it is possible to simplify shapes and arrangements of the electric syringe pumps 27 and 28, the electric switching valves, the pump blocks 31 and 32 containing the pump nozzles 29 and 30, etc. Further, by effecting such a simple operation that the
25 cartridge is sandwiched between the pump blocks 31 and 32 at the same time while ensuring necessary chambers and passages, it is possible to inject the pump

nozzles 29 and 30 and simplify the structure of the pump blocks 31 and 32. Further, all the nozzle ports 4a to 4t are disposed at an identical level, i.e., are arranged linearly, whereby all the heights of the
5 passages 14a to 14t connected to the nozzle ports 4a to 4t become equal to each other. As a result, preparation of the passages 14a to 14t becomes easy.

Further, in the treatment apparatus shown in Figure 7, in the case where the length of the pump
10 blocks 31 and 32 is increased n times the original length with respect to n biochemical reaction cartridges, when ~~the~~ n cartridges are arranged in series, it is possible to perform a necessary step with respect to all the n cartridges at the same time.
15 As a result, a biochemical reaction can be performed in ~~the~~ a large number of biochemical reaction cartridges with a very simple apparatus structure.

When the tester performs the steps of flowing of the solution into the chamber and hermetically sealing
20 the chamber described with reference to Figures 4 and 5 and then inputs a treatment start instruction at the input unit 33, the bar code label applied to the biochemical reaction cartridge is first read by the bar code reader (not shown) of the
25 treatment apparatus. In the treatment apparatus, treatment sequences necessary for the respective types of cartridges are memorized in advance. When the type

of cartridge is identified by the read bar code, the contents and procedures of treatment necessary for the cartridge are automatically determined to start the treatment. When the bar code cannot be read or the
5 read bar code is not a predetermined bar code, the tester can also manually input treatment steps by the input unit 33.

~~Figure 8 (consisting of Figures 8A and 8B) is~~
show a flow chart for explaining an example of a
10 treatment procedure in the treatment apparatus in this embodiment.

Referring to Figure 8A, in ~~a~~ step S1, the first hemolytic agent is moved from the solution storage chamber 6a to the chamber 11a of the reaction portion
15 1 by ~~effecting injection of~~injecting the solution and hermetic sealing, as described with reference to Figures 4 and 5. In ~~a~~ step S2, the control unit 26 opens only the nozzle ports 4a and ~~4b~~4k, and air is discharged from the electric syringe pump 27 and
20 sucked in the reaction portion 1 from the electric syringe pump 28, whereby the first hemolytic agent is injected from the chamber 11a into the chamber 16 containing blood. At this time, by controlling air suction ~~of air~~ from the pump 28 so as to start 10 -
25 200 msec after initiation of the air discharge from the pump 27, the solution can flow smoothly without ~~causing splashing~~causing splashing or scattering ~~thereof~~ at its leading

end, although ~~it~~ this depends on ~~a~~ the viscosity of the hemolytic agent and a resistance of the passage.

As described above, by shifting the timing of the supply and suction of air so as to control a manner ~~of~~
5 in which the pressure is application-applied and ~~pressure reduction~~ reduced, it is possible to cause the solution to flow smoothly. In a preferred embodiment, the solution can be caused to flow ~~further~~ even more smoothly by ~~effecting such a controlling~~ that a degree
10 ~~of~~ air suction ~~of air~~ from the electric syringe pump 28 such that it is linearly increased from the initiation of the air discharge from the pump 27. Further, it becomes possible to alleviate the pressure generated in the reaction portion 1 by applying and reducing
15 pressure in combination. As a result, it is also possible to ~~achieve such an effect that the solution is prevented intentionally prevent the solution from~~ flowing into a branched passage or chamber ~~in the case during the movement thereof where the solution is not~~
20 ~~intended to flow into the branched passage or chamber during movement thereof. These are~~ This is also true in the case of a subsequent liquid movement.

The air supply control can be readily realized by using the electric syringe pumps 27 and 28. More
25 specifically, after only the nozzle ports 4a and 4o are opened, discharge and suction of air are repeated alternately by the syringe pumps 27 and 28 to cause a

repetitive flow and ~~flowback~~-return of the solution of the chamber 6 in the passage 19, thus stirring the solution. Alternatively, the solution can be stirred while continuously discharging air from the pump 28 to
5 generate bubbles.

Figure 9 is a sectional view of the reaction portion 1 shown in Figure 6 along a ~~cross~~-cross-section intersecting the chambers 11a, 16 and 11k, and shows such a state that the nozzle port 4a is
10 pressurized by injecting therein the pump nozzle 29 and the nozzle port 4k is reduced in pressure by injecting therein the pump nozzle 30, whereby the first hemolytic agent in the chamber 11a flows into the chamber 16 containing blood.

15 Referring again to Figure 8A, in ~~a~~-step S4, only the nozzle ports 4b and 4k are opened and the second hemolytic agent in the chamber 11b is caused to flow into the chamber 16 in the same manner as in the case of the first hemolytic agent. Similarly, in ~~a~~-step
20 ~~S5~~S6, the magnetic particles in the chamber 11c, after being moved from the chamber 6c to the chamber 11c, are caused to flow into the chamber 16. In ~~the~~-steps S4 and S6, stirring is performed in the same manner as in ~~the~~-step S2. In ~~the~~-step S6, DNA resulting from
25 dissolution of cells in ~~the~~-steps S2 and S4 attaches to the magnetic particles.

Thereafter, in ~~a~~-step S7, an electromagnet 23 is

turned on and only the nozzle ports 4e and 4k are opened. Then, air is discharged from the electric syringe pump 28 and sucked in from the pump 27 to move the solution from the chamber 16 to the chamber 11e.

5 At the time of movement, the magnetic particles and DNA are trapped in the passage 19 on the electromagnet 23. The suction and discharge by the pumps 27 and 28 are alternately repeated to reciprocate the solution two times between the chambers 16 and 11e, whereby a
10 trapping efficiency of DNA is improved. The trapping efficiency can be further improved by increasing the number of reciprocations. In this case, however, ~~it takes a longer treating time by that much~~the time of treatment is increased by the amount of time it takes
15 to perform the additional reciprocations.

As described above, DNA is trapped in a flowing state on such a small passage having a width of about 1 - 2 mm and a height of about 0.2 - 1 mm by utilizing the magnetic particles, so that DNA can be trapped
20 with a high efficiency. This is also true for RNA and proteins.

Then, in ~~a~~step S8S9, the electromagnet 23 is turned off, and only the nozzle ports 4f and 4l are opened. Thereafter, air is discharged from the
25 electric syringe pump 28 and sucked in from the pump 27 to move the first extraction cleaning liquid from the chamber 11l to the chamber 11f. At this time, the

magnetic particles and DNA trapped in ~~the~~ step S7 are moved together with the extraction cleaning liquid, whereby cleaning is performed. After the reciprocation ~~of~~ is performed two times ~~is performed~~
5 in the same manner as in ~~the~~ step S7, the electromagnet 23 is turned on, and the reciprocation ~~of~~ is similarly performed two times ~~is similarly performed~~ to recover the magnetic particles and DNA in the passage 19 on the electromagnet 23 and return the
10 solution to the chamber 11l.

In ~~a~~ step S11, cleaning is further performed in the same manner as in ~~the~~ step S5 by using the second extraction cleaning liquid in the chamber 11m, after being moved from the chamber 6m to the chamber 11m in
15 ~~a~~ step S10, in combination with the nozzle ports 4f and 4m.

In ~~a~~ step 12, the eluent is moved from the chamber 6d to the chamber 11d. In ~~a~~ step S13, only the nozzle ports 4d and 4o are opened while the
20 electromagnet 23 is kept on~~7~~ and air is discharged from the pump 27 and sucked in from the pump 28, whereby the eluent in the chamber 11d is moved to the chamber 17.

At this time, the magnetic particles and DNA are
25 separated by the action of the eluent, so that only the DNA is moved together with the eluent to the chamber 17, and the magnetic particles remain in the

passage 19. Thus, extraction and purification of the DNA are performed. As described above, the chambers 11l and 11m containing the extraction cleaning liquids and the chamber 11f containing a waste liquid after
5 the cleaning are separately provided, so that it becomes possible to effect extraction and purification of the DNA in the biochemical reaction cartridge.

Next, in a-step S14, the PCR agent is moved from the chamber 6g to the chamber 11g. In a-step S15,
10 only the nozzle ports 4g and 4o are opened, and air is discharged from the electric syringe pump 27 and sucked in from the pump 28 to cause the PCR agent in the chamber 11g to flow into the chamber 17. Further, only the nozzle ports 4g and 4t are opened, and air
15 discharge and suction by the pumps 27 and 28 are repeated alternately to cause repetitive flow and flow-back of the solution of the chamber 17 in the passage 20, thus stirring the solution~~the solution in the chamber 16 to flow into the passage 20.~~
20 Thereafter, ~~the returning operation is repeated to effect stirring.~~ Then, the Peltier element 24 is controlled to retain the solution in the chamber 17 at 96 °C for 10 min. Thereafter, a cycle of heating at 96 °C/10 sec, 55 °C/10 sec, and 72 °C/1 min. is
25 repeated 30 times, thus subjecting the eluted DNA to PCR to amplify the DNA.

In a-step S16, only the nozzle ports 4g and 4t

are opened, and air is discharged from the electric syringe pump 27 and sucked in from the pump 28 to move the solution in the chamber 17 to the chamber 18. Further, by controlling the Peltier element 25, the
5 solution in the chamber 18 is kept at 45 °C for 2 hours to effect the hybridization. At this time, discharge and suction of air by the pumps 27 and 28 are repeated alternately to move the solution between the chamber 18 and the passage 15t, which effects
10 stirring of the solution in the chamber 18 to the passage 15t. ~~Thereafter, the hybridization proceeds while effecting stirring by repeating the returning operation.~~

Then, after the first cleaning liquid is moved
15 from the chamber 6h to the chamber 11h in a step S17, in a step S18, while keeping the temperature at 45 °C, only the nozzle ports 4h and 4r are opened, and air is discharged from the electric syringe pump 27 and sucked in from the pump 28 to cause the first cleaning
20 liquid in the chamber 11h to flow into the chamber 11r through the chamber 18 while moving the solution in the chamber 18 to the chamber 11r. The suction and discharge by the pumps 27 and 28 are repeated alternately to reciprocate the solution two times
25 between the chambers 11h, 18 and 11r and finally return the solution to the chamber 11h. Thus, the fluorescence-labeled specimen DNA and the fluorescence

label, which are not hybridized, are cleaned.

Figure 10 is a sectional view of the reaction portion 1 shown in Figure 6 along a ~~cross~~-cross-section intersecting the chambers 11h, 18 and 11r.

5 The reaction portion 1 is pressurized by injecting the pump nozzle 29 into the nozzle port 4h and ~~is reduced~~
~~in the pressure~~ is reduced by injecting the pump nozzle 30 into the nozzle port 4r. Figure 10 illustrates
such a state that the first cleaning liquid is caused
10 to flow into the chamber 11r through the chamber 18.
The chamber 11h actually communicates with the solution storage portion 2, but in Figure 10, it is
illustrated as a ~~state in which it does not~~
~~communicate~~ communicating with the solution storage
15 portion 2 by providing a ceiling thereof, for the
convenience of ~~explanation~~ explaining the structure.

Referring ~~again~~ to Figure 8B, after the second cleaning liquid is moved from the chamber 6j to the chamber 11j in a step S19, in a step S20, while
20 keeping the temperature at 45 °C, the cleaning is further effected in the same manner as in ~~the step S10~~
S18 by using the second cleaning liquid in the chamber 11j in combination with the nozzle ports 4j and 4r, and the solution is finally returned to the chamber
25 11j. As described above, the chambers 11h and 11j containing the cleaning liquids and the chamber 11r containing the waste liquid after the cleaning are

separately provided, so that it becomes possible to
~~effect extraction and purification~~ purify (clean) of
the biological material on the DNA microarray 21 in
the biochemical reaction cartridge.

5 After alcohol is moved from the chamber 6i to the
chamber 11i in a step S21, in a step 22, only the
nozzle ports 4i and 4r are opened, and air is
discharged from the electric syringe pump 27 and
sucked in from the pump 28 to move alcohol in the
10 chamber 11i to the chamber 11r through the chamber 18.
Thereafter, only the nozzle port 4i and 4t are opened,
and air is discharged from the pump 27 and sucked in
from the pump 28 to dry the inside of chamber 18.

 Thereafter, when the tester operates a lever (not
15 shown), the pump blocks 31 and 32 are moved away from
the biochemical reaction cartridge. As a result, the
pump nozzles 29 and 30 are removed from the nozzle
ports 4 of the cartridge. Then, the tester mounts the
cartridge in a DNA microarray reader ~~for DNA~~
20 ~~microarray~~, such a known scanner, to effect perform
the measurement and analysis.

 In the above-described embodiment, the
identification of the cartridge is performed by using
the bar code label, but may also be performed by using
25 a two-dimensional bar code, an IC chip, PFID ~~RFID~~
(radio frequency identification), etc. Further, on
the basis of external dimensions of the cartridge,

such as height and length, the number of recesses or projections provided on the side surfaces, the upper surface and the lower surface of the cartridge, and a combination thereof, the type of the cartridge can be
5 identified in various ~~manner~~ways. As a result, it is possible to attain a similar effect.

In the above embodiment, the identification of the cartridge is performed and based on the identified type of the cartridge, and the treatment steps are
10 set. However, it is also possible to set a treatment sequence on the basis of the information, ~~on the~~ contents and procedures of the treatment steps, which are written in the two-dimensional bar code or the like. Further, in the case of changing testing
15 conditions, such as a reaction time, cartridge by cartridge, different treatment steps are written in a two-dimensional bar code and the bar code is adhered to the cartridge, whereby it becomes possible to effect a desired reaction step with reliability.

20 As described ~~herein~~above, the biochemical reaction cartridge according to the present invention has a reaction portion including a chamber and a passage and a solution storage portion, which is isolated or separated from the reaction portion, for
25 storing a solution, such as a reagent or a cleaning agent, and is constituted by such a member that it is separated for moving the solution from the solution

storage portion to the reaction portion and is
penetrable, or that it is a penetrable member disposed
at a boundary wall portion between the solution
storage portion and the reaction portion, which
5 contact each other. As a result, respective solutions
can be prepared with the biochemical reaction
cartridge immediately before the respective treatment
steps, so that the biochemical reaction cartridge has
the advantage of causing an intended reaction properly
10 without causing a reagent in a chamber to flow into a
passage or another chamber even when an environmental
change or vibration occurs during a treatment step
using another solution.

Further, particularly, a step of moving each of
15 the solutions in the solution storage portion to the
reaction portion immediately before ~~use~~ing the
solutions is employed, so that it is possible to
reliably effect ~~reliable~~the reaction without causing
the solutions to flow into adjacent chambers and
20 passages even when ~~vibration of~~ the treatment
apparatus ~~occurs~~vibrates or there ~~arises~~is an error
~~of~~in pressure control during treatment in each of the
steps.

Further, the treatment apparatus automatically
25 reads the bar code label applied to the biochemical
reaction cartridge and identifies the type of the
cartridge, thus automatically setting necessary

treatment steps. Accordingly, it becomes possible to simply effect the treatment with reliability since it is not necessary for the operation to set a complicated treatment procedure on all such occasions
5 that there ~~are~~is a plurality of cartridge types.

Further, since the biochemical reaction cartridge of the present invention has the above-described structure, it is possible to prepare a solution therein as desired. As a result, the biochemical
10 reaction cartridge eliminates the inconvenience of replenishing a reagent and reduces an error in selection of the type of reagent. In addition, even when an environmental change or vibration ~~is caused to~~ occursat the time of storage and conveyance, the
15 reagent in the chamber does not flow into a passage or another chamber. Accordingly, the biochemical reaction cartridge can appropriately cause ~~an~~the intended reaction~~appropriately~~.

While the invention has been described with
20 reference to the structures disclosed herein, it is not ~~confined~~limited to the details set forth and this application is intended to cover such modifications or changes as may come within the purposes of the improvements or the scope of the following claims.

ABSTRACT OF THE DISCLOSURE

A biochemical reaction cartridge includes a reaction portion, comprising a chamber and a passage,
5 for effecting a biochemical reaction, and a solution storage portion, which is isolated or separated from said reaction portion, for storing a solution in a position corresponding to the chamber. The cartridge is provided with a penetrable partition member
10 disposed between ~~said~~ the solution storage portion and ~~said~~ the reaction portion, so as to move the solution from ~~said~~ the solution storage portion to the chamber of ~~said~~ the reaction portion. The biochemical reaction cartridge is incorporated in a biochemical
15 reaction apparatus.